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ALEXANDRIA, VIRGINIA 22314-2700
703 837-9600

REMARKS

The Office Action of September 29, 2003 has been carefully considered.

Initially, Applicants feel compelled to comment on the opening statement in the Office Action that "[T]he examiner does not understand why the Applicants are adding new claims that have the same subject matter as the claims that were rejected several times. Rather than amending the claims to overcome the rejections, the applicants prolong prosecution time of the application by adding similar claims that have already been rejected... New claims must be canceled."

To make it perfectly clear, claims 37-40 were added in the previous amendment to provide a *separate* set of claims in which the method included the administration of conjugated equine estrogens. This was done so that upon appeal of the claims, there would be a separate issue regarding claims 37-40. However, claims 37-40 have now been canceled; claim 30 has also been canceled.

Claims 25, 27-30, 33, 34 and 36-40 have been rejected under 35 USC 112, 1st paragraph, on the basis that the specification, "while being enabling for administering the combination of nomegestrol and estradiol in a continuous on intermittent fashion, from 21-25 days per month (see lines 4-6, on page 4 of the specification), does not reasonably provide enablement for 'continuously without interruption... The question is unlimited time in claim. How long will be 'continuous.' Specification discloses i.e. 21-25 days so claims must be limited to no. of days supported by disclosure."

Applicants believe that the Office Action has not properly interpreted the specification. The initial disclosure of the administration is provided in the second

complete paragraph on page 3 of the specification:

"The combined treatment is more often used in a continuous fashion, i.e. without interruption. However, some people are in favour of using it in an intermittent fashion, for example 25 days per month..."

Two methods of administration are therefore disclosed, one being defined as *continuous*, the other being defined as *intermittent*, the intermittent method being exemplified by administration 25 days per month.

These two methods of administration are repeated in the discussion of the invention on page 4 of the specification, where it is stated that "[T]he compositions according to the invention based on nomegestrol and free or esterified estradiol or equine conjugated estrogens are administered in a continuous or intermittent fashion, from 21-25 days per month."

If this paragraph is interpreted based on the clear and unambiguous disclosure on page 3, it can only mean that in a first method, there is continuous administration without interruption, and in a second method, administration is from 21 to 25 days per month.

It is the method of continuous administration without interruption which is found in Example II, beginning on page 7 of the specification. In Example II, there is administration of nomegestrol acetate and estradiol every day for the course of the study, 24 weeks.

Nevertheless, the Office Action states that the "specification discloses i.e. 21-25 days so claims must be limited to no. of days supported by the disclosure."

Moreover, the Office Action states that since "all the showing and discussions were based on continuous administration without bleeding, the invention as claimed does

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not find support by the disclosure of the invention."

However, as should be clear from the above discussion, both the claims and the examples of the specification are directed to the embodiment in which the administration in continuous, without interruption, and not to the *separate and distinct embodiment* in which administration is interrupted, and takes place for 21-25 days per month.

As both the specification and claims provide support for continuous administration without interruption, withdrawal of this rejection is requested.

Claims 25, 27-30, 33, 34 and 36-40 have been rejected under 35 USC 112, 1st paragraph, on the basis that the specification is enabling for estradiol, but does not provide enablement to make and use the specification commensurate with these claims.

The Office Action alleges that "[C]laims are not limited to the scope to the extent of support in disclosure so that one skilled in the art without undue experimentation can practice invention" and further states that "[A] disclosure should contain representative examples, which provide reasonable assurance to one skilled in the art that the compounds fall within the scope of a claim will posses the alleged activity."

It is further noted that the Office Action states that "the invention provides a method of treating estrogenic deficiencies in women comprising administering without interruption combination of 0.5 to 3 mg of an estrogenic compound and 1.5 to 3.75 mg of nomegestrol acetate."

The invention as presently claimed *does not* recite administering an "estrogenic compound" but rather recites administering "an estrogen selected from the group consisting of free and esterified estradiol" (claim 34 has been amended

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hereinabove to utilize proper Markush group language). The term "free and esterified estradiol" represents a limited class of compounds; in order to provide evidence of this, Applicants have attached hereto an entry from the Merck Index, Tenth Edition (1983) for estradiol, as well as entries for α-estradiol, and estradiol esters, estradiol benzoate and estradiol 17β-cypionate. The essential chemical formula for estradiol remains the same throughout, and it is well known in the art to claim salts and esters of pharmaceutical compounds without a specific example for every salt and ester claimed.

The present specification *does* contain representative examples that provide reasonable assurance that the *claimed compounds* (free and esterified estradiol) will possess the alleged activity. Example II of the specification reports on the administration of both a free estradiol, 17β-estradiol, and an estradiol ester, estradiol valerate. Given that the term "estradiol" represents only a limited class of compounds, no reason is seen why the two examples reported should not provide reasonable assurance to one of ordinary skill in the art that the invention functions as disclosed in the specification.

Indeed, in the Office Action of February 8, page 8, 2000, the Examiner alleged that estradiol valerate would have the same properties as estradiol unless unexpected results are shown. The Office Action now takes the contrary position that the behavior of estradiol esters cannot be predicted and these compounds cannot be claimed unless proof is submitted that such compounds do have the same behavior.

With regard to conjugated equine estrogens, these compounds have been canceled from the claims. Nevertheless, Applicants point out that such compounds are well known in the art, and are represented by a commercially available product

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sold under the name Premarin. Moreover, a combination of conjugated equine estrogens and a progestogen has been sold under the trademark Prempro®.

Given that estradiol and its esters represent a limited and well known class of compounds, and given that representative compounds were tested as part of the present application, Applicants submit that the present specification is enabling within the meaning of 35 USC 112, 1st paragraph, and withdrawal of this rejection is requested.

Claims 24, 25, 27-30, 33, 34, and 36-40 stand rejected under 35 USC 103 over Plunkett et al in view of Fraser et al.

Plunkett et al discloses a method for treatment of menopausal disorder comprising continuous administration of a progestogen in combination with estrogen, where the estradiol can be administered continuously or intermittently. While estradiols and their esters are disclosed, the only examples are directed to cyclic or intermittent administration of estrogens. Nomegestrol acetate is not disclosed.

Fraser et al discloses administration of nomegestrol acetate for 12 days per month, in combination with an estradiol implant. *All women treated with this regimen experienced withdrawal bleeding* in contrast to the claimed invention in which there is no withdrawal bleeding. Given that Plunkett et al has the object of minimizing withdrawal bleeding, Applicants submit that one of ordinary skill in the art would not have been led, based on Fraser et al, to combine nomegestrol acetate with estradiol with the expectation of eliminating withdrawal bleeding.

With regard to the declaration of Dr. Thomas submitted with the previous amendment, the Office Action poses the question of how much estradiol and nomegestrol acetate was used in each case. The information can be obtained by

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reference to Fraser et al and the present specification. In Fraser et al, tests were conducted using 50 mg estradiol implants (daily dose not disclosed), and daily doses of 0.5, 1.0 and 2.5 mg of nomegestrol acetate. According to the present specification, tests were conducted with daily doses of 1.5 mg of 17β-estradiol and 2 mg estradiol valerate, and 2.5 mg of nomegestrol acetate.

However, as noted in the declaration, Fraser et al does not enable one of ordinary skill to draw conclusions about the use of nomegestrol acetate in hormone replacement therapy because the estradiol plasma levels were very high and the nomegestrol was given for 12 days of a cycle. This was an unusual design for a sequential HRT combination, and was only a model to check the short term effects of different doses of nomegestrol acetate on the endometrium. Since withdrawal bleeding was observed by Fraser et al, it would not be expected that estradiol and nomegestrol acetate could be given according to the invention without withdrawal bleeding. Indeed, little can be concluded from Fraser et al, since the methodology is much different from the usual HRT methodology.

Finally, with regard to Table 3 of the declaration, Applicants note that nomegestrol acetate has been known for about 25 years, and a number of articles have been published reporting on studies of the properties of this compound. The Examiner should consider the invention to be what has been claimed, i.e. a method for treating estrogenic deficiencies in post menopausal women while avoiding the appearance of osteoporosis and withdrawal bleeding, by continuously without interruption administering to the women a composition containing from 0.5 to 3 mg of an estrogen selected from the group consisting of free or esterified estradiol and 1.5 to 3.75 mg of nomegestrol acetate by daily dose.

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As the Fraser et al reference does not suggest to one of ordinary skill in the art that a daily dose without interruption of nomegestrol acetate in combination with estradiol will result in satisfactory HRT treatment *without withdrawal bleeding*, Applicants submit that the claimed invention is patentable over the cited art, and withdrawal of this rejection is requested.

In view of the foregoing amendments and remarks, Applicants submit that the present application is now in condition for allowance. An early allowance of the application with amended claims is earnestly solicited.

Respectfully submitted,

Ira J. Schultz
Registration No. 28666

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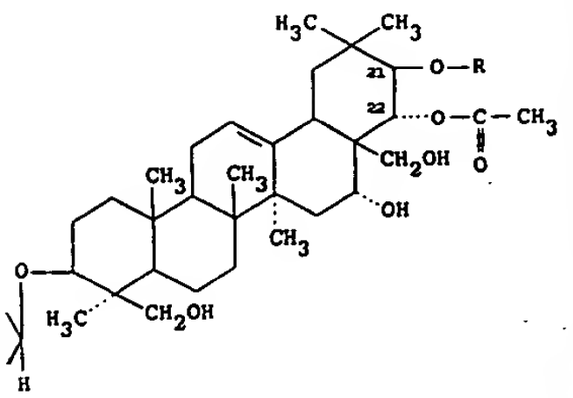
ler, *Arzneimittel-Forsch.* **10**, 273 (1960); *nn.* **669**, 171 (1963). Recent structural the two major glycosides in the mixture e aglycon, *protoescigenin*, which is acyla-ic acid, and from the sugar moiety, glu-wo D-glucose molecules. The two agly-the C-21 position which is acylated by *q.v.* or tiglic acid, *q.v.* Structure and ste-i, Tschesche, *Tetrahedron* **25**, 415 (1969); *eimittel-Forsch.* **20**, 205 (1970); *eidem, Z.* , 1133 (1970). Early work identified two *β-escin*: Wagner, Basse, *ibid.* **320**, 27 *prosaponin B* with β-escin: Voigtlander, *nittel-Forsch.* **13**, 385 (1963). β-Escin is id can be converted to α-escin: Wagner, at. **3,450,691** (1969 to Klinge); Wagner *et rsch., loc. cit.* Pharmacology: Hampel *et* (1970); Lang, Mennicke, *ibid.* **22**, 1928 Tschesche, Wulff in *Fortschr. Chem. Org.* 6 (1973).

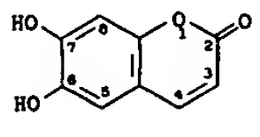


R = tiglic acid or angelic acid

Major glycosides of Escin

phous powder, mp 225-227°. $[\alpha]_D^{25}$ methanol). Very sol in water. Hemolytic LD_{50} in mice, rats, guinea pigs: 320, 720, ; 3.2, 5.4, 15.2 mg/kg i.v.
p 251-252°.
acyl. Leaflets from dil ethanol, mp 222-° (c = 5 in methanol). Practically insol in index: 1:40,000. LD_{50} in mice, rats, gui-, 188 mg/kg orally; 1.4, 2.0, 7.2 mg/kg i.v. treatment of peripheral vascular disorders.

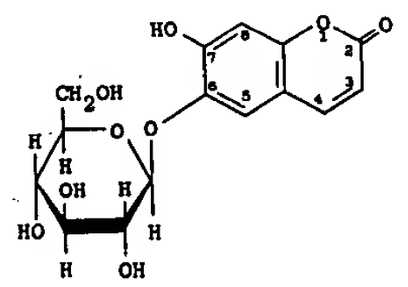
in. *6,7-Dihydroxy-2H-1-benzopyran-2-one; marin;* cichorigenin. $C_9H_6O_4$; mol wt %, H 3.40%, O 35.93%. The aglucon of es-riin. By hydrolysis of esculin or of cicho-*h. Pharm.* 270, 486 (1932). By synthesis: bner, *Ber.* 32, 288 (1899); Bert, *Compt.* 1942). *Review:* Sethna, Shah, *Chem. Rev.*



glacial acetic acid; leaflets by vacuum sub-68-270°. Soluble in dil alkalies with blue derately sol in hot alcohol and in glacial st insol in ether, in boiling water.
for absorption of ultraviolet light.

a. *6-(β-D-Glucopyranosyloxy)-7-hydroxy-*

side; esculoside; bicolorin; enallachrome; polychrome; Escosyl. $C_{15}H_{16}O_9$; mol wt 340.28. C 52.94%, H 4.74%, O 42.32%. In leaves and bark of horse chestnut tree *Aesculus hippocastanum* L., *Hippocastanaceae.* Extraction procedure: Tumann, *Chem. Zentr.* **1916**, I, 1277. Synthesis: Merz, Hagemann, *Naturwiss.* **29**, 650 (1941); *eidem, Arch. Pharm.* **282**, 79 (1944); Amiard, Nominé, *Bull. Soc. Chim. France* **1948**, 476.



Sesquihydrate, needles from hot water, mp 204-206°. $[\alpha]_D^{18}$ −78.4° (c = 2.5 in 50% dioxane). One gram dissolves in 580 ml water, 13 ml boiling water. Sol in hot alcohol, methanol, pyridine, ethyl acetate, acetic acid. Aq solns show blue fluorescence above pH 5.8. Absorption spectrum: Merz, *Arch. Pharm.* **270**, 482 (1932); Goodwin, Pollock, *Arch. Biochim. Biophys.* **49**, 1 (1954). Has vitamin P activity.

Pentaacetate dihydrate, needles from methanol, mp 163-164°.

4-Methylesculin, $C_{16}H_{18}O_9$. Prepn: Velluz, Amiard, *Bull. Soc. Chim. France* **1948**, 1109.

THERAP CAT: Skin protectant.

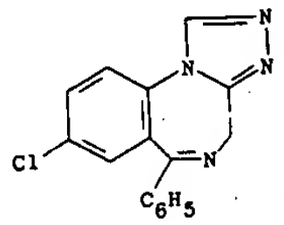
3643. Esparto Wax. Spanish grass wax; halfa wax. A wax derived from a tall, tough grass of the Mediterranean region (S. Europe and N. Africa and Libya). The grass is shipped to Scotland, where it is dewaxed and made into fine paper. The wax is a byproduct. Two species of grass are cultivated for their excellent cellulose content: *Stipa tenacissima* L. *(Macrochloa tenacissima* (L.) Kunth.), *Graminaceae* and *Lygeum spartum* L., *Graminaceae. Constit.* Esparto wax consists of 15-17% free wax acids, 20-22% alcohols and hydrocarbons, 63-65% esters. The principal hydrocarbon is hentriacontane ($C_{31}H_{64}$, mp 68°). The acids include cerotic, montanic, myricinic ($C_{30}H_{60}O_2$, mp 68°), lacceric ($C_{32}H_{64}O_2$, mp 70.5°) and hydroxy acids: A. H. Warth, *Chemistry and Technology of Waxes* (Reinhold, New York, 1947) p 139.

Hard, tough wax. d_4^{25} 0.9887. mp 78.1°. Solidifies at 68.8°. Acid value 23.9. Saponification value 69.8. Soly in ethanol (25°): 0.244 g/100 ml; in ethylene chloride (37°): 1.48 g/100 ml.

USE: Substitute or extender for carnauba wax, *q.v.* Blends well with other waxes. Emulsifies easily and imparts smoothness to polishes. Preferred in the manufacture of carbon papers.

3644. Essential Fatty Acids. EFA. Essential dietary constituents belonging to the linoleic acid family. G. O. Burr and M. M. Burr described expts with albino rats which led them to conclude that in animals given a ration extremely poor in fat, a deficiency disease results which can be cured by linoleic or linolenic acids, *q.q.v.*, and arachidonic acid, *q.v.*, or fats contg these acids (such as lecithin from soybeans): *J. Biol. Chem.* **82**, 345 (1929); **86**, 587 (1930). Support for the conception of the essential nature of these two fatty acids was contained in two reports by Evans and Lepkovsky, *J. Biol. Chem.* **96**, 143, 157 (1932). It was stated that growth would not take place unless unsaturated fatty acids with two or more double bonds were present in the ration. In 1934 a series of three papers by Evans, Lepkovsky, and Murphy appeared, in which the name *vitamin F* was given to the above unsaturated fatty acids. There was a short period of commercial exploitation of vitamin F. Following investigations made by the American Medical Association in 1937, the term "vitamin F" became discredited. At the request of the Council on Foods and Nutrition of the American Medical Association, Hansen and Burr discussed the essentiality of fatty acids in human nutrition in their article "Essential Fatty Acids and Human Nutrition," *J. Am. Med. Assoc.* **132**, 855 (Dec. 7, 1946), in which they state: "In regard to clinical observations made thus far with human subjects, there is no evidence to indicate that a lack of the essential fatty acids produces a disturbance in growth, hematuria, kidney lesions, impaired reproduction or lactation, and sterility, which abnormalities, are attributed to the dietary lack of either linoleic or arachidonic acid in small experimental animals." *See also* the extensive reviews by Deuel and Greenberg in *Fortschr. Chem. Org. Naturst.* **6**, 1-86 (1950); Stangl, *Int. Rev. Vitamin Res.* **23**, 164-207 (1951); Rahm, Holman, *The Vitamins*, W. H. Sebrell, R. S. Harris, Eds., **vol. 3** (Academic Press, New York, 1971) pp 303-339; W. H. Kunan, *Angew. Chem. Int. Ed.* **15**, 61 (1976); J. F. Mead, "Nutrients with Special Functions: Essential Fatty Acids" in *Human Nutrition, A Comprehensive Treatise*, **vol. 3A**, R. Alfin-Slater, D. Kritchevsky, Eds. (Plenum Press, New York, 1980) pp 213-238. Book: *Essential Fatty Acids and Prostaglandins*, R. J. Holman, Ed. (Pergamon Press, New York, 1982) 968 pp.

3645. Estazolam. *8-Chloro-6-phenyl-4H-[1,2,4]triazolo-[4,3-a][1,4]benzodiazepine; 8-chloro-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine;* D-40TA; Esilgan; Eurodin; Julodin; Nuctalon. $C_{16}H_{11}ClN_4$; mol wt 294.75. C 65.20%, H 3.76%, Cl 12.03%, N 19.01%. Prepn: Hester, Ger. pat. **2,012,190** corresp to U.S. pat **3,701,782** (1970, 1972 to Upjohn); Meguro, Kuwada, *Tetrahedron Letters* **1970**, 4039; *eidem*, Ger. pat. **1,955,349** (1971 to Toyama), *C.A.* **74**, 88078t (1971); Tawada *et al.*, Ger. pat. **2,114,441** (1971 to Takeda), *C.A.* **76**, 34320p (1972); Hester *et al., J. Med. Chem.* **14**, 1078 (1971). Structure-activity studies: Nakajima *et al., Japan. J. Pharmacol.* **21**, 489 (1971). Pharmacology: *eidem, ibid.* 497 and *Takeda Kenkyusho Ho* **31**, 349 (1972). Metabolism: Tanayama *et al., Xenobiotica* **4**, 33-64 (1974); *see also ibid.* 229, 441. Molecular structure studies: Kamiya *et al., Chem. Pharm. Bull.* **21**, 1520 (1973).



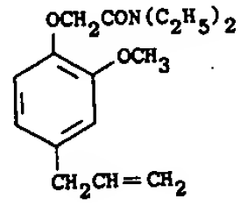
Crystals from ethyl acetate-Skellysolve B hexanes, mp 228-229° (Hester, *loc. cit.*). LD_{50} orally in male mice, rats and rabbits: 740, 3200, 300 mg/kg, Yokotani *et al., Takeda Kenkyusho Ho* **32**, 152 (1973), *C.A.* **79**, 133006j (1973).

THERAP CAT: Hypnotic; sedative.

3646. Ester Gums. These are the glyceryl, methyl, and ethyl esters of rosin acids. They are made by heating rosin and the alcohol under pressure until condensation takes place. The gums are insol in water, but sol in amyl acetate, some oils, turpentine, carbon tetrachloride, etc.

USE: Instead of copal, damar, or kauri in making enamels, paints, cellulose lacquers, and particularly with tung oil for waterproof varnishes.

3647. Estil. *N,N-Diethyl-2-[2-methoxy-4-(2-propenyl)-phenoxy]acetamide; 2-(4-allyl-2-methoxyphenoxy)-N,N-diethylacetamide; N,N*-diethyl-2-methoxy-4-allylphenoxyacetamide; 2-methoxy-4-allylphenoxyacetic acid *N,N*-diethylamide; 2-M-4-A; G 29505; Detrovel. $C_{16}H_{23}NO_3$; mol wt 277.35. C 69.28%, H 8.36%, N 5.05%; O 17.31%. Prepn: **Brit.** pats. **792,490; 837,995** (1958, 1960 to Geigy).

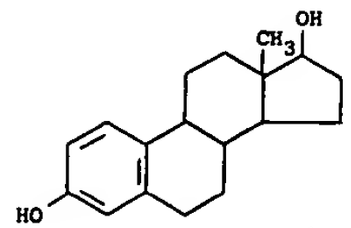


Oil. $bp_{0.001}$ 143-146°; n_D^{25} 1.5300. Soluble in water, pH of 5% aq soln 7.3.

THERAP CAT: Anesthetic.

3648. Estradiol. *Estra-1,3,5(10)-triene-3,17-diol; β-*

estradiol; α-estradiol (obsolete); *cis*-estradiol; 3,17-epidihydroxyestratriene; dihydrofollicular hormone; dihydrofolliculin; dihydroxyestrin; dihydrotheelin; Compudose 365; Dihydromenformon; Dimenformon; Diogyn; Estrovite; Femestral; Gynergon; Gynoestryl; Lamdiol; Macrodiol; Oestergon; Ovahormon; Ovasterol; Ovocyclin; Ovocylin; Perlatanol; Primofol; Profoliol; Progynon-DH. $C_{18}H_{24}O_2$; mol wt 272.37. C 79.37%, H 8.88%, O 11.75%. The most potent naturally occurring estrogen in mammals; formed by the ovary, placenta, testis and possibly by the adrenal cortex. Has been isolated from follicular liquor of sow ovaries; from pregnancy urine of mares. Isoln: MacCorquodale *et al., J. Biol. Chem.* **115,** 435 (1936). Numerous prepns from other steroids, *e.g.,* Butenandt, Georgens, *Z. Physiol. Chem.* **248,** 129 (1937); Hildebrandt, Schwenk; Logemann, Koester; Inhoffen; U.S. pats. **2,096,744; 2,225,419; 2,361,847** (1938, 1941, 1944 all to Schering); Inhoffen, Zühlsdorff, *Ber.* **74,** 1914 (1941). Total syntheses: U. Eder *et al., Ber* **109,** 2948 (1976); W. Oppolzer, D. A. Roberts, *Helv. Chim. Acta* **63,** 1703 (1980). Comprehensive description of the valerate ester: K. Florey, Ed. in *Analytical Profiles of Drug Substances* vol. 4 (Academic Press, New York, 1975) pp 192-208.



Prisms from 80% alc, stable in air, mp 173-179°. $[\alpha]_D^{25}$ +76 to +83° (dioxane). uv max: 225, 280 nm. Precipitated by digitonin. Almost insol in water; freely sol in alcohol; sol in acetone, dioxane, other organic solvents; solns of fixed alkali hydroxides; sparingly sol in vegetable oils. 1 mg = 10,000 international units.

3-Benzoate, *see* separate entry.

17β-Cypionate, *see* separate entry.

17-Propionate, $C_{21}H_{28}O_3$, *Acrofollin, Akrofollin,* mp 199-200°, *See* Miescher, Scholz, *Helv. Chim. Acta* **20,** 263 (1937); U.S. pats. **2,160,555; 2,233,025** (1939, 1941 to Ciba).

Dipropionate, $C_{24}H_{32}O_4$, *Agofollin, Dimenformon Dipropionate, Diovocylin, Ovocyclin Dipropionate, Ovocyclin-P, Progynon-DP.* mp 104-105°; Miescher, Scholz, U.S. pats. **2,160,555; 2,205,627; 2,233,025** (1939, 1940, 1941 to Ciba).

Hemisuccinate, $C_{22}H_{28}O_5$, *Eutocol.*

17-Heptanoate, $C_{25}H_{36}O_3$, *estradiol enanthate, SQ 16150.* Crystals from diisopropyl ether, mp 94-96°, Gauthier *et al., Ann. Pharm. Franc.* **16,** 757 (1958).

17-Undecanoate, $C_{29}H_{44}O_3$, *estradiol undecylate, Delestrec.*

17-Undecenoate, $C_{29}H_{42}O_3$, small plates, mp 105-106°. $[\alpha]_D^{20}$ +42° (chloroform). uv max: 280-282 nm (log ε 3.30). Prepn: Ringold *et al.,* U.S. pat. **2,990,414** (1961 to Syntex).

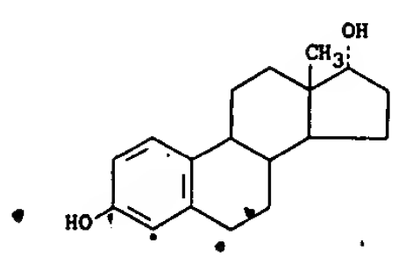
17-Valerate, $C_{23}H_{32}O_3$, *Delestrogen, Progynova.* Crystals, mp 144-145°, Miescher, Scholz, U.S. pats. **2,205,627; 2,233,025.**

Note: A mixture of estradiol with medroxyprogesterone 17-acetate is marketed as *Provest.*

THERAP CAT: Estrogen.

THERAP CAT (VET): Estrogenic hormone therapy.

3649. α-Estradiol. *Estra-1,3,5(10)-triene-3,17α-diol;* 1,3,5-estratriene-3,17α-diol; 3,17-dihydroxyestratriene. $C_{18}H_{24}O_2$; mol wt 272.37. C 79.37%, H 8.88%, O 11.75%. Has been isolated from pregnancy urine of mares. Prepn from β-estradiol by inversion of the hydroxyl group at C-17 after tosylation: Allais, Hoffmann, U.S. pat. **2,835,681** (1958).

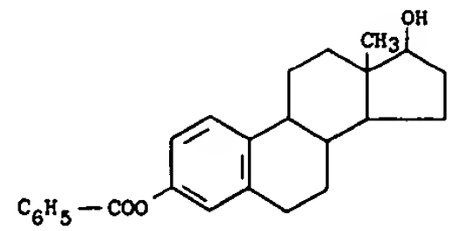


Needles with ½H_2O from 80% alcohol, mp 220-223°. $[\alpha]_D^{20}$ +53° to +56° (c = 0.9 in dioxane). Not precipitated by digitonin (in 80% alcoholic soln). Soluble in alcohol, acetone, aq alkalies. One gram dissolves in more than 100 ml of boiling benzene. Slightly sol in ether, chloroform. Insol in water, aq dil acids.

Diacetate, $C_{22}H_{28}O_4$, mp 140-142°.

3-Benzoate, $C_{25}H_{28}O_3$, mp 156-157°; also reported as polymorphous: I, mp 63°; II, mp 153°; III, mp 158°.

3650. Estradiol Benzoate. β-Estradiol-3-benzoate; oestradiol monobenzoate; Benovocylin; Benzhormovarine; Benzoestrofol; Benzofoline; Benzo-Gynoestryl; de Graafina; Diffolisterol; Difolliculine; Dimenformon benzoate; Diogyn B; Eston-B; Femestrone; Follicormon (ampuls); Follidrin (ampuls); Graafina; Gynécormone; Hidroestron; Hormogynon; Motovar; Oestroform; Ovasterol-B; Ovex B; Ovocyclin Benzoate; Ovocyclin M; Ovocyclin-MB; Primogyn B; Primogyn I; Progynon-B; Progynon Benzoate; Recthormone Oestradiol; Solestro; Unistradiol. $C_{25}H_{28}O_3$; mol wt 376.50. C 79.75%, H 7.50%, O 12.75%. Preparation: Schwenk, Hildebrandt, U.S. pat. **2,054,271** (1936 to Schering-Kahlbaum); Sandulesco, Brit. pat. **485,388** (1938 to Lab. Franc. Chimiother.).



Crystals from alc, mp 191-196°. Stable in air. $[\alpha]_D^{25}$ +58 to +63° (c = 2 in dioxane). Sol in alc, acetone, dioxane; slightly sol in ether, vegetable oils. 1 mg = 10,000 international estradiol benzoate units. Precipitated by digitonin.

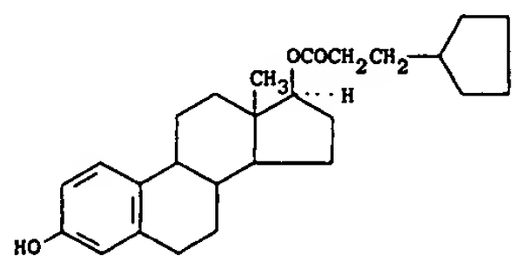
17β-Maltoside heptaacetate, $C_{51}H_{62}O_{20}$, dec 227-229°. $[\alpha]_D^{20}$ +56° (methanol). Sol in water; very sol in glucose solns: Meystre, Miescher, *Helv. Chim. Acta* **27,** 235 (1944).

17β-Maltoside hydrate, $C_{30}H_{44}O_{12}.H_2O$, dec 272-282°. $[\alpha]_D^{20}$ +52° (c = 1.07 in methanol). Sol in water; very sol in glucose solns: *eidem, ibid.* 1154, 1157.

THERAP CAT: Estrogen.

THERAP CAT (VET): Estrogenic hormone therapy.

3651. Estradiol 17β-Cypionate. Estradiol 17β-cyclopentanepropionate; estradiol 17β-cyclopentylpropionate; ECP; Depoestradiol; Depofemin; Estradep. $C_{26}H_{36}O_3$; mol wt 396.55. C 78.74%, H 9.15%, O 12.10%. Prepd by treating estradiol 3,17β-dicyclopentanepropionate with potassium carbonate: Ott, U.S. pat. **2,611,773** (1952 to Upjohn).

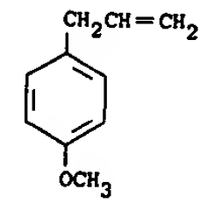


Crystals from benzene + petr ether, mp 151-152°. $[\alpha]_D^{25}$ +45° (chloroform). Sol in ether, methanol, benzene, chloroform, peanut oil, cottonseed oil, corn oil, sesame oil. The limit of soly in the oils is about 400 mg/ml. Thixotropic gels may be prepd by adding aluminum monostearate to the oil solns.

THERAP CAT: Estrogen.

THERAP CAT (VET): Estrogenic hormone therapy.

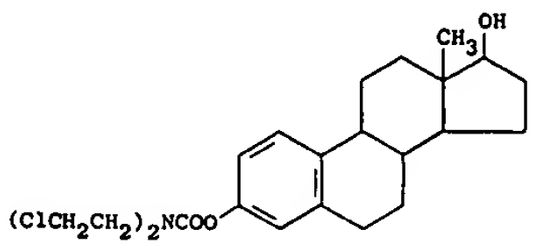
3652. Estragole. *1-Methoxy-4-(2-propenyl)benzene; p-allylanisole;* chavicol methyl ether; esdragol. $C_{10}H_{12}O$; mol wt 148.20. C 81.04%, H 8.16%, O 10.80%. Main constituent of *tarragon oil (estragon oil),* the oil from *Artemisia dracunculus* L., *Compositae* (esdragon) where it occurs to an extent of 60-75%: Grimaux, *Bull. Soc. Chim.* [3] **11,** 34 (1894); Daufresne, *ibid.* [4] **3,** 333 (1908). Occurs also in pine oil and in American turpentine oil. Prepn: Tiffeneau, *Compt. Rend.* **139,** 482 (1904); Verley, Ger. pat. **154,654;** D. Wigfield, K. Taymaz, *Tetrahedron Letters* **1973,** 4841; P. Gramatica *et al., Gazz. Chim. Ital.* **104,** 629 (1974).



Liquid. d_4^{21} 0.9645. bp_{764} 216°; bp_{25} 108-114°; bp_{12} 95-96°. $n_D^{17.5}$ 1.5230. Sol in alcohol, chloroform. Forms azeotropic mixtures with water. LD_{50} orally in rats, mice: 1820, 1250 mg/kg, P. M. Jenner *et al., Food Cosmet. Toxicol.* **2,** 327 (1964).

USE: In perfumes and as flavor in foods and liqueurs.

3653. Estramustine. *Estra-1,3,5(10)-triene-3,17-diol 3-[bis(2-chloroethyl)carbamate]; estradiol 3-bis(2-chloroethyl)carbamate;* estra-1,3,5(10)triene-3,17β-diol 3-[*N,N*-bis(2-chloroethyl)carbamate]; Ro 21-8837. $C_{23}H_{31}Cl_2NO_3$; mol wt 440.41. C 62.72%, H 7.10%, Cl 16.10%, N 3.18%, O 10.90%. Estradiol to which nitrogen mustard is bound. Prepn: Belg. pat. **646,319** corresp to Fex *et al.,* U.S. pat. **3,299,104** (1963, 1967, to Leo). Niculescu-Duvaz *et al., J. Med. Chem.* **10,** 172 (1967). Clinical results: Anderes, *Praxis* **60,** 1375 (1971); Muntzing, Nilsson, *Z. Krebsforsch. Klin. Onkol.* **77,** 166 (1972).



Crystals from benzene-petr ether, mp 104-105°. $[\alpha]_D^{20}$ +50° (in dioxane). uv max (alcohol): 270.7, 276.5 nm.

17-Phosphate, $C_{23}H_{32}Cl_2NO_6P$, *Estracyt.* mp 155° (dec). $[\alpha]_D^{20}$ +30° (dioxane). Sol in aqueous and alkali solns.

17-(Dihydrogenphosphate), disodium salt, $C_{23}H_{30}Cl_2NNa_2O_6P$, *Emcyt.*

THERAP CAT: Antineoplastic.

3654. Estriol. *Estra-1,3,5(10)-triene-3,16,17-triol;* 1,3,5-estratriene-3β,16α,17β-triol; 3,16α,17β-trihydroxy-$\Delta^{1,3,5}$-estratriene; 16α-hydroxyestradiol; follicular hormone hydrate; oestriol; trihydroxyestrin; Aacifemine; Destriol; Hormomed; Klimoral; Oekolp; Ovesterin; Ovestin; Theelol; Tridestrin; Triovex. $C_{18}H_{24}O_3$; mol wt 288.37. C 74.97%, H 8.39%, O 16.64%. A metabolite of, and considerably less potent than 17β-estradiol *(q.v.).* It is usually the predominant estrogenic metabolite found in urine. During pregnancy the placenta produces relatively large amounts of estriol. Isoln from human pregnancy urine: Marrian, *Biochem. J.* **23,** 1090, 1233 (1929); probably occurs as a glycuronide: Cohen, Marrian, *ibid.* **29,** 1577 (1935). Isoln from human placenta: Collip, *Brit. Med. J.* **1930, II,** 1080; Collip *et al., Endocrinology* **18,** 71 (1934). Also obtained from plant sources. Isoln from pussywillows: Skarzynski, *Nature* **131,** 766 (1933). Structure: Huffman, Lott, *J. Am. Chem. Soc.* **69,** 1835 (1947). Crystal and molecular structure: Cooper *et al., Acta Crystallogr.* **25B,** 814 (1969). Partial synthesis: Huffman, *J. Biol. Chem.* **169,** 167 (1947). Syntheses: Huffman, Lott, *J. Am. Chem. Soc.* **71,** 719 (1949); Leeds *et al., ibid.* **76,** 2943 (1954).

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